

## Scientific Abstract

**A phase II/III, multi-center, open-label, randomized study to compare the effectiveness and safety of intralesional administration of RPR/INGN 201 in combination with Taxotere<sup>®</sup> and carboplatin and radiotherapy versus Taxotere<sup>®</sup> and carboplatin and radiotherapy alone in patients with locally advanced unresectable non small cell lung cancer (NSCLC)**

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Lung cancer remains the worldwide leading cause of cancer deaths in both men and women. In the United States alone, an estimated 177,000 new cases were diagnosed and 158,700 deaths occurred in 1996. Non-small-cell histologies account for approximately 80% of lung cancer cases. A small number of patients with locoregionally advanced disease (stage III) may be cured by combined modality approaches. Despite significant gains achieved with the combined modality approach in advanced NSCLC, survival rates remain low because local and distant treatment failures are common.

The primary objective of this protocol is to determine if the intralesional administration of RPR/INGN 201 in conjunction with primary chemoradiation therapy improves loco-regional tumor control and survival in patients with locally advanced nonresectable NSCLC. Assuming a median survival time of 15.5 months with chemoradiation alone, the goal of the trial is to improve this by at least 25%, to 19.4 months.

The study will be organized as a multi-center, open-label, randomized two-arm phase II/III trial of concomitant chemotherapy (Taxotere/carboplatin) + radiation either with or without adjuvant intralesional RPR/INGN 201 for treatment of patients with unresectable stage II or III non-small cell lung cancer. The two treatment arms consist of:

Study treatment arm A: RPR /INGN 201 + Taxotere<sup>®</sup> + Carboplatin + Radiation Therapy

Study treatment arm B: Taxotere<sup>®</sup> + Carboplatin + Radiation Therapy

Treatment will be as follows for the four modalities:

- RPR/INGN 201 administration (Arm A only)

RPR/INGN 201 will be administered day 1, three days ( $\pm 1$  day) prior to the start of chemoradiation therapy (day 4) and on the first day of the third and fifth weeks of radiation therapy (day 18 and day 32).

RPR/INGN 201 will be given at a daily dose of  $2 \times 10^{12}$  vp as a mix with dextrose 5% water (D5W) adjusted to the tumor largest diameter. A single injection in the center of the accessible tumor will be administered for lesions  $\leq 4$  cm (3ml total volume) in largest diameter. For larger lesions, additional injection(s) will be given in a region of the tumor beyond the 4 cm radius and the final volume administered will be 10ml. The dose ( $2 \times 10^{12}$  viral particles) and volume will remain unchanged during the treatment period.

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RPR/INGN 201 will be delivered by fine needle injection directly into the tumor by bronchoscopy or percutaneously via CT scan guidance.

- Chemotherapy administration (both Arms)

Taxotere® will be given as a one hour IV infusion weekly at a dose of 20mg/m<sup>2</sup> per day with carboplatin AUC-2 before radiation on days 4, 11, 18, 25, 32, 39 and 46 for a treatment duration of 6 1/2 weeks, with standard care according to local routine.

- Radiation Therapy (both Arms)

Radiation Therapy will be started on day 4 and administered at 2Gy daily five times a week for 6 and a half weeks for a total dose of 66 Gy.

Each patient will receive one course of treatment, and patients' primary tumor will be biopsied at three months following the completion of study treatment, including radiotherapy.

This is a randomized two arm study with randomization balanced on the prognostic factor of whether the patient has stage II or stage III disease. The two patient outcomes used for monitoring and treatment evaluation are local control, LC, defined as negative biopsy of the primary tumor at 3 months following completion of the study treatment, and survival time, T. Both LC and T will be used as the basis for monitoring and decision making throughout the trial. A novel Bayesian design will be used to conduct the study in order to reduce the time for decisions and the number of patients required to prove superiority. This design is based on the underlying probability mixture of the two sequential outcomes of interest, namely, freedom from loco-regional progression, and secondarily, overall survival. Interim decision making will be conducted at 8, 12, and 18 months to assess futility or superiority and thus permit a seamless transition from phase II to phase III unless the addition of RPR/INGN 201 appears inferior. The number of patients required for this study is between a minimum of 160 and a maximum of 900, depending on the true impact of locoregional failure upon survival (which is not known). Under a conventional group sequential phase II to phase III design, using the same assumed margins of therapeutic effect, more patients would be required and the studies would take longer. Under the proposed design, the study will last approximately 35 months.

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